Interleukin-6 and soluble interleukin-2 receptor alpha – markers of inflammation in patients with psoriatic arthritis?

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ABSTRACT

Objective. To evaluate a possible systemic effect of joint inflammation in contrast to skin disease only, by measuring IL-6 and IL-2sRα.

Methods. Two hundred and nineteen patients (111 male / 108 female, age 50.4±14.5 years (mean±SD)) with psoriasis were clinically and laboratory examined. 134 patients had inflammatory joint manifestations defined as peripheral arthritis and/or axial disease, of whom 37 had measurable inflammation, defined as ESR >25 mm/h and/or CRP >15 mg/L.

Results. Interleukin-6 was significantly higher in patients with joint disease and measurable inflammation ((median, Q1-Q3) 4.07, 0.92-14.60), and in patients without measured inflammation (1.22, 0.70-3.46), compared to patients with skin disease only (0.70, 0.70-1.73, p<0.001 and p=0.002 respectively). The difference between the two groups of patients with inflammatory joint manifestations was significant (p=0.001). The levels of IL-6 correlated with the actual number of joints affected with arthritis (p<0.001; r=0.248), ESR (p<0.001; r=0.459), CRP (p<0.001; r=0.314) and IL-2sRα (p=0.002; r=0.210). The levels of IL-2sRα did not differ between the 3 groups.

Conclusion. In this study, IL-6 was significantly higher in patients with psoriasis and inflammatory joint disease with or without routine measurable inflammatory activity compared with patients having psoriasis of the skin. We found that patients with psoriasis and joint inflammation may have systemic effects that could be captured by serum measurements of IL-6. Soluble IL-2Rα was not a marker of inflammation in this study.

Introduction

Psoriatic arthritis (PsA), an inflammatory joint disease associated with psoriasis, presents with a heterogeneous pattern of conditions expressed by different manifestations, such as mild mono-arthritis, severe erosive and destructive polyarthritis indistinguishable from rheumatoid arthritis, and spondylarthropathy with axial involvement or enthesitis. The disease pattern often differs between patients as well as within the same patient over time. To date the most commonly used classification has been that of Moll and Wright from 1973 (1) with five subgroups (distal interphalangeal (DIP) joint involvement, spondylitis, mono-oligoarthritis, polyarthritis and arthritis mutilans) identified and which also describes the most common disease patterns. However, this classification does not include manifestations such as undifferentiated spondylarthropathy (uSpA), and enthesitis or dactylitis, often present in PsA (2).

Laboratory measured parameters, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are insensitive for evaluation of inflammation in patients with PsA and are often within the normal range despite advanced joint disease (1, 3). Other variables related to, and of importance in inflammation, e.g., different cytokines, have been studied (4). So far, increased levels of tumour necrosis factor alpha (TNF-α) in serum, synovial fluid and skin lesions of psoriasis have been reported (4). Furthermore, the TNFA and TNFB genes are reported to be associated with psoriasis and psoriatic arthritis (5, 6). Increased serum levels of interleukin (IL)-10, IL-6, IL-1 receptor antagonist (IL-1ra) and soluble IL-2 receptor-alpha (IL-2sRα) have been reported in patients with PsA (7, 8).

The aim of this cross-sectional study was to evaluate a possible systemic effect on joint inflammation in contrast to skin disease only by measuring the soluble IL-2sRα and the pro-inflammatory cytokine IL-6.

Material and methods

Blood samples were collected from 219 patients (111 males / 108 females, age 50.4±14.5 years (mean ± SD), see Table I) with psoriasis and the corresponding sera stored. Skin involvement was evaluated and all patients were clinically examined for inflammatory joint manifestations defined as peripheral arthritis, axial disease and/or enthesitis (PsA). Peripheral arthritis was diagnosed when a swollen and tender joint, with duration of more than 6 weeks, located outside the spine and/or...
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sacroiliac joints, was present. Polyarthritic disease was defined as more than four swollen and tender joints present at the time for the examination. The number of tender and swollen joints was counted according to the ACR 68/66 joint index (9). The diagnosis of axial disease was based on radiological sacroiliitis graded according to the New York criteria (≥ grade 2) (10) and/or syndesmophytes, ligamentous ossification, vertebral squaring and shining corners of the spine (11). Dactylitis and enthesitis were evaluated as defined by Helliwell and Wright (2). The affected skin area was graded using a five point scale; from no actual lesion to extensive involvement. The activity of the skin involvement (erythema, induration, and scaling) was graded using four grades as: no activity to severe. When using the Moll and Wright criteria (1), 85 patients had skin disease only (Group 1). Of the 134 patients with PsA, 97 patients had no measurable inflammation (Group 2) and 37 patients had measurable inflammation defined as ESR > 25 mm/h and/or CRP > 15 mg/L (Group 3) (Table I).

Erythrocyte sedimentation rate (mm/h, Westergren) and CRP (mg/L) were measured using routine methods, and the detection level for CRP was 10 mg/L. IL-2sR (detection level = 0.7) (0.70-1.73) (0.70-3.46) (0.92-14.60) 0.001

ESR, mm/h, mean (SEM) 9.88 (1.06) 10.6 (0.63) 36.1 (3.15) <0.001

CRP, g/L, median (Q1-Q3) (detection level = 10)
(10.00-10.00) (10.00-10.00) (10.00-28.50) <0.001

IL-2sR, pg/ml, mean (SEM) 885.57 (73.95) 884.09 (54.93) 880.78 (102.92) ns

IL-6, pg/ml, median (Q1-Q3) (detection level = 0.7)
(0.70-1.73) (0.70-3.46) (0.92-14.60) 0.001

Table I. Patients diagnosed as having PsA according to the Moll and Wright criteria.

<table>
<thead>
<tr>
<th>No joint manifestations</th>
<th>Joint manifestations with increased ESR and/or CRP</th>
<th>Joint manifestations with increased ESR and/or CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years, mean (SD)</td>
<td>51.2 (14.9)</td>
<td>47.8 (13.1)</td>
</tr>
<tr>
<td>Duration of skin disease, years, mean (SD)</td>
<td>24.98 (14.07)</td>
<td>23.87 (14.0)</td>
</tr>
<tr>
<td>Duration of joint disease, years, mean (SD)</td>
<td>15.6 (11.98)</td>
<td>17.76 (15.95)</td>
</tr>
</tbody>
</table>
| Number of joints with peripheral arthritis, mean (SEM) | 2.14 (0.29) | 4.11 (0.79) | 0.02
| Patients with polyarthritic disease, % | 43.3 | 86.5 | <0.001
| RF-positive patients (%) | 4.9 | 6.3 | 0.02
| ESR, mm/h, mean (SEM) | 9.88 (1.06) | 10.6 (0.63) | 36.1 (3.15) |
| CRP, g/L, median (Q1-Q3) (detection level = 10) | 10.00 | 10.00 | 17.00 |
| IL-2sR, pg/ml, mean (SEM) | 885.57 (73.95) | 884.09 (54.93) | 880.78 (102.92) |
| IL-6, pg/ml, median (Q1-Q3) (detection level = 0.7) | 0.70 | 1.22 | 4.07 |

ns: not significant.
< comparison between the two groups with joint manifestations.
< comparison between group 1 and group 2.

Statistics

Differences between continuous data were tested using the Students t-test and the Mann-Whitney ranking test when the parameters were analysed with detection levels. The Chi-square test was performed for differences between categorical data and the Spearman rank-order equation was used to identify correlations.

Results

Interleukin-6 was significantly higher both in patients with PsA (defined according to the Moll and Wright criteria) and concurrent increased ESR and/or CRP, and those patients without increased routine parameters of inflammation, compared with patients with skin disease only (p<0.001 and p=0.002 respectively; see Table I). The differences in IL-6 levels between the two groups of patients with joint manifestations was also significant (p=0.001). Polyarthritic disease pattern was more common in the group with measurable inflammation compared with the patients without measurable inflammation (p<0.001; Table I). Patients with DIP-joint involvement had significantly increased levels of IL-6 compared with patients without DIP-joint involvement ((median, (Q1-Q3) 3.13, (0.71-13.69) vs 0.70, (0.70-2.81), p<0.001). The IL-6 levels were also significantly higher in patients with dactylitis compared to patients without dactylitis (2.45, (0.70-8.42) vs 0.70, (0.70-3.08), p=0.011). The presence of RF was significantly more common in patients with increased ESR/CRP (Group 3; p=0.047; Table I) but the presence of RF was not associated with increased levels of IL-6 (p=0.151). Furthermore, when excluding RF-positive patients from the analysis, the results were almost identical with the result from the whole group with no differences in significant values (data not shown). No difference in
extent and activity of the skin disease was found between the three groups of patients (data not shown). Considering the patients within the 2 groups with joint disease, there were no differences in joint disease or its duration, or treatment with DMARDs/NSAIDs between the groups (data not shown).

The levels of IL-6 correlated with the actual number of joints affected with arthritis ($p<0.001$; $r_{s}=0.248$), ESR ($p<0.001$; $r_{s}=0.459$), CRP ($p<0.001$; $r_{s}=0.314$) and IL-2sRα ($p=0.002$; $r_{s}=0.210$) (Table II). The levels of IL-2sRα did not differ between the groups of patients although there were correlations with number of actual peripheral arthritis ($p=0.026$; $r_{s}=-0.152$) and IL-6 ($p=0.002$; $r_{s}=0.210$) (Table II).

Recently, new classification criteria have been proposed by the CASPAR (Classification of Psoriatic Arthritis) project, an international undertaking to update and validate the diagnostic and classification criteria for PsA (12). Of the patients with PsA according to the CASPAR-criteria, the same patients had measurable inflammation, as by the criteria of Moll and Wright (n=37) whilst 112 had no measurable inflammation. Interleukin-6 was significantly increased in patients with joint disease and measurable markers of inflammation (4.07, 0.79-14.60), as well as in patients without measured inflammation (1.03, 0.7-3.35) compared with patients with skin disease only (0.70, 0.70-2.12; $p<0.001$ and $p=0.019$, respectively). The difference between the two groups of patients with joint disease was also significant ($p<0.001$).

**Discussion**

In this study, IL-6 was significantly higher in patients with psoriasis and inflammatory joint disease irrespective of the presence of increased measurable routine inflammatory variables (ESR and/or CRP) compared with patients having psoriasis but without joint manifestations. The level of IL-6 was highest in the patient group with increased ESR and/or CRP. Interleukin-6 correlated with these variables and with the number of joints affected by actual arthritis and sIL-2Rα. Patients with psoriasis and joint inflammation have systemic effects that could be identified by measurement of serum IL-6 irrespective of routine laboratory analyses. Soluble IL-2sRα was not evident as a marker for inflammation in this study.

The newly proposed CASPAR criteria (12) are still not fully validated and in order to compare the Moll and Wright criteria and CASPAR criteria we also classified the patients to the new classification. The CASPAR criteria include patients with enthesitis and dactylitis while the Moll and Wright criteria only include patients with arthritis. The two classification systems identified the same individuals with joint inflammation and increased routine laboratory detectable variables. However, 15 more patients with enthesitis were included as having joint manifestation and diagnosed with PsA according to the CASPAR criteria, but the analysis of IL-6 and IL2sRA showed similar results in the two classification systems. It was apparent that RF was more common in PsA patients with laboratory measurable inflammation although there were no association with IL-6 or IL2sRA. It seems that this marker may have some impact on the disease course since it is known that increased ESR/CRP is a marker of a more severe joint disease in PsA patients. The patients in this study were not evaluated for the diagnostic criteria for RA and some of the patients in this study would undoubtedly fulfil the criteria for RA.

However, it is more likely that the presence of RF may represent a greater contribution of the immune system and a more severe disease course.

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